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Prostate Cancer: Evaluation of Response to Treatment, Response Criteria, and the Need for Standardization of the Reporting of Results

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Abstract—*Response criteria and the reporting of results in clinical trials on drug therapy of stage D prostate cancer were evaluated by examination of studies listed in the* Index Medicus *1980–1984. During this 5-year period, 70 studies (51 phase II and 16 phase III) were listed, comprising 3184 evaluable patients. Among 346 patients reported as having evaluable disease according to the WHO criteria, 198 had well-defined evaluable disease. A variety of response criteria were used, the NPCP criteria being the most frequent. Only three studies included solely patients with evaluable disease according to the WHO criteria. Reporting of results was often inadequate. The value of the most frequently used response parameters such as acid phosphatase, bone scan, per-rectal ultrasound, CT scan, bone pain and performance status is discussed. A system to standardise the reporting of results is proposed.*

INTRODUCTION

PROSTATE cancer is the second most frequent cancer in the male population of the Western World. Approximately 50% of the patients have metastatic disease at diagnosis. The disease has its highest incidence in men over the age of 70. Often it is a slowly progressive disease, and death is frequently caused by other non-malignant disease. Byar reported 42% deaths from other causes in stage D patients [1].

During the clinical course of the disease, metastases are most frequently (85%) localized to the bones [2], and the bone marrrow is involved in 1/3 of patients with positive radiographs [3]. Lung metastases diagnosed on chest X-ray have in retrospective studies been reported in only 6% of patients with advanced disseminated disease [4], and peripheral lymph node metastases accessible to measurement are found in only 5% of the cases [5].

In many cases, progression is slow and may take place intermittently with shorter or longer periods of clinical stability. Objective response in bone metastatic disease is difficult to assess, making the time of progression in stable disease an uncertain parameter for response.

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In advanced stages, many of these patients suffer from bone pain. Castration or systemic estrogen treatment are established palliative methods of treatment for these patients. In addition, local radiation therapy may induce pain relief in a substantial number of the patients. The search to find alternative treatment for advanced disseminated disease necessitates a new appraisal of the criteria of response to treatment and the methods of reporting results in clinical trials.

Two major systems for evaluating response in phase II trials in stage D prostate cancer have emerged. The traditional system established by the World Health Organization (WHO) has finally been adopted by the European Organization on Research on Treatment of Cancer Urological Group (EORTC GU-Group) [6], and is also part of the U.S.A.'s National Prostatic Cancer Project (NPCP) criteria (Table1) [7]. The EORTC GU-Group does not currently include the primary tumor as a measurable lesion in phase II trials, and the only accepted measurable lesions (tumor masses) are subcutanous nodules, palpable lymph nodes, nodular lung lesions and lymph nodes and liver metastases measured by CT scan or ecchography [6]. Bone metastases are regarded as evaluable disease. The EORTC GU-Group recommends only patients with measurable disease for phase II studies [6]. The NPCP allows the prostate and hepatomegaly and liver function tests as evaluable parameters. In contrast to the

Table 1. Response criteria according to the NPCP [7]

Response	Tumor masses	Acid phosphatase	Bone metastases osteolytic	Bone metastases osteosclerotic	Hepatomegaly & liver function	Symptoms: pain performance	Other
Complete*	disappeared	normalized	recalcified	disappeared	normalized	no deterioration	
Partial*	≥50% reduction	normalized	recalcified	no progression	≥30% reduction	no deterioration	
Stable*	<25% increase	decreased	no progression	no progression	<30% increase	no deterioration	
Progression	>25% increase		new lesions			deterioration	anemia ureteral obstruction

*If present, all parameters.

EORTC GU-Group, the NPCP consider stabilization of the disease activity a category of objective response [7].

For phase III studies, survival defined as the time from the day of the first treatment to death, metastases-free interval and time to progression are the usable parameters applied when comparing various treatments. When using these parameters, it is important to consider prognostic factors for stratification in order to avoid selection of particular prognostically favorable or unfavorable patients for a particular treatment.

As not all investigators are using the above accepted evaluation criteria, the studies published in the years 1980–1984 (listed in the *Index Medicus*) were examined with regard to their methodology and the reporting of results.

MATERIALS AND METHODS

All clinical studies on drug therapy of prostate cancer reported in the Englsih literature and listed in *Index Medicus* in a 5-year period (1980–1984) were analysed. Only the most updated results on a certain regimen from the same investigational group were included in the evaluation. Case reports and two symposia proceedings (*Scand. J. Urol. Nephrol.* **55** (Suppl.), 1980 and *Urology* **23** (6 Suppl.), 1984) were excluded. A total of 70 studies, including 28 studies on chemotherapy only, 24 on hormone therapy only, and 18 on both were examined.

The following data from each study were collected: type of study, treatment modality, number of evaluable patients, response criteria, methods of evaluation, number of patients with measurable disease, the location of the measurable lesions and the method used to report the results.

RESULTS

Among the 70 studies included in this analysis 54 were phase II trials and 16 were phase III trials. The number of evaluable patients entered into these studies are indicated in Table 2. A total of 3184 patients were regarded as evaluable for response according to a variety of different response criteria. Only 346 patients (11%) (Table 3) had disease evaluable according to the WHO criteria. Among these, no information was given concerning metastatic site in 92 patients, and five had non-specified soft tissue metastases, while 51

Table 2. Distribution of evaluable patients on 70 phase II and III studies listed in the Index Medicus *1980–1984*

No. of patients	No. of studies phase II	phase III
	54	16
< 10	5	0
10–19	12	0
20–49	30	6
50–99	7	3
100–246	0	7
No. of evaluable patients	1572	1612

Table 3. Measurable or evaluable disease according to the WHO criteria reported in 70 studies

	No. of patients
Lymph nodes and subcutis	84
Lung and mediastinum	108
Pelvis and retroperitoneum	16
Soft tissue	5
Liver	51
Not specified	92
Total	346/3184 (11%)
Response	66

Tale 4. Response criteria used in 70 studies

	No. of studies
NPCP	29 (41%)
WHO	3 (4%)
Local disease only	4
Survival only	1
Other (inc. local disease 15)	23
Inadequately defined	10

patients had liver metastases. Thus, only 198 patients (6%) were left as having well defined, evaluable disease according to the WHO criteria. As shown in Table 4, only three studies (4%) solely included patients evaluable according to the WHO criteria [8–10], whereas 29 (41%) used the NPCP criteria. In another 27 studies, evaluable soft tissue metastases were reported as a part of the evaluable parameters. The localization of soft tissue metastases was not specified in six of these studies. Other response criteria usually included prostatic size, bone metastases on bone scan and $\geq 50\%$ reduction in increased acid phosphatase. Pain was the main parameter for evaluating response in 23 studies. In 10 studies, response criteria were insufficiently defined.

Treatment results on accessory NPCP response parameters such as pain, bone scan, radiographic bone survey and acid phosphatase were only reported specifically in a minority of the studies (Table 5). In none of the studies was an evaluation of the variations in the pre-treatment bone pain performed, and in only two studies was a sufficient documentation of the method of pain evaluation and the degree of pain relief given. The pre-treatment magnitude of acid phosphatase was taken into consideration in two studies. The causes of death other than prostate cancer were not reported in any of the randomized studies using survival as the final goal for treatment effect. Palliative treatments—surgical or radiation—during protocol treatment were not indicated in any of the studies. Among 68 studies in which response, including stable disease, was reported, response duration or time to progression was reported in 24 (35%).

DISCUSSION

Despite attempts to define strict response criteria during the past decade, the present study indicates that the majority of papers on the effect of treatment in disseminated prostate cancer inadequately describe response parameters. The major reason is undoubtedly due to low frequency of measurable disease and insufficient methods for evaluation of the primary tumor or bone metastatic disease.

Table 5. Results reported on accessory NPCP response parameters

	No. of studies
Pain: adequately reported on*	2
inadequately reported on	16
Bone scan	19
Radiographic bone survey	6
Acid phosphatase	33

*An adequate report on pain response included an indication of the pain level before the start of treatment and the number of patients who had a defined reduction in pain level.

Serum acid phosphatase is elevated in approximately 75% of patients with bone metastases [11]. Moderate correlation has been found between reduction in acid phosphatase and clinical response [11, 12]. However, because of rather large and unpredictable fluctuations [13], a normalization of acid phosphatase is mandatory if the enzyme is used as response parameter. As pointed out by the NPCP, an additional concomitant response has to be demonstrated, e.g. on radiographic bone survey.

Several attempts have been made to quantify response on bone scintigrams [14–18]. The overall impression is that some correlation exists between scintigraphic response and clinical response or response in acid phosphatase. On the contrary, there seems to be poor correlation between scintigraphic and radiographic response with much fewer radiographic responses than scintigraphic responses [17, 18]. Thus, Levenson *et al.* concluded that the lack of sensitivity and paradoxical worsening of the disease with scan improvement in some patients implies that scans are not accurate enough to be employed as the sole test in following patients with bone disease [17]. However, good correlation seems to exist between progression of bone disease on bone scans and of extra-osseous disease [17]. The interpretation of bone scans is made difficult by the scan to scan variation due to technical circumstances. Finally, increase in intensity in a given lesion might reflect recalcification (response?) rather than being an expression of disease progression. So far, no study has been performed in order to evaluate the technical scan to scan variation in prostate cancer.

Evaluation of the primary site as response parameter also presents difficulties. Digital exploration is the usual method to examine the prostate. The size and shape of a cancerous prostate may objectively be difficult to define or may be so small or even of normal size that evaluation is unfeasible. During recent years, attempts have been made to measure the size of the prostate by per-rectal

Table 6. The ECOG criteria for evaluation of performance status and pain

Performance status
0. Normal activity, no symptoms
1. Symptoms but ambulatory
2. In bed < 50% of time
3. In bed > 50% of time
4. 100% bedridden
Pain
0. None
1. Mild (peripheral-acting analgesics such as acetylsalisylic acid)
2. Moderate (occasionally narcotics)
3. Severe (oral narcotics permanently)
4. Very severe (parental narcotics)
5. Uncontrollable

ultrasound [18–21]. The method seems to be reproducible with little scan to scan variation [21].

The value of computerized tomography (CT scan) in the evaluation of local disease and regional lymph node metastases remains to be evaluated. Golimbu *et al.* found two false positive among seven patients with metastatic pelvic lymphnodes on CT scan using lymphadenectomy as end-point [22]. The frequency of pelvic and paraortic lymph node metastases on CT scan has yet to be assessed.

According to the NPCP, subjective response criteria include bone pain and performance status evaluated according to the Eastern Cooperative Oncology Group (ECOG) criteria (Table 6), but these parameters are difficult to assess. The pain level may vary considerably from day to day and may spontaneously subside in one focus and appear or progress in another at the same time even without treatment. Apparently the variation in pain level has never been studied in detail in patients with prostate cancer and bone pain. However, it is important to know the individual variation in pain level before using this as a parameter for response, and all pain foci must be accurately evaluated before and during therapy. The overall performance status of these often very old patients is frequently not only influenced by the prostate cancer, but also by other variables such as age and other medical problems. Thus, an improvement in performance status during treatment due to concomitant adjustment of other medical or psychosocial problems should be excluded if one wishes to use this parameter.

The NPCP has included stable disease as part of the response category after having shown that the survival of patients with stable disease was similar to patients who responded to treatment [23]. The time of progression, however, is difficult to assess exactly due to fluctuations in pain and acid phosphatase and stability of radiological abnormalities in patients with only bone metastases. As indicated in Fig. 1, the explanation for the better survival of patients with stable disease compared to patients with a more rapid progression may alternatively be that the stable category is a selected subpopulation of the non-responding category with a displacement of the time for progression in relation to the start of treatment or a slower progression rate and there-

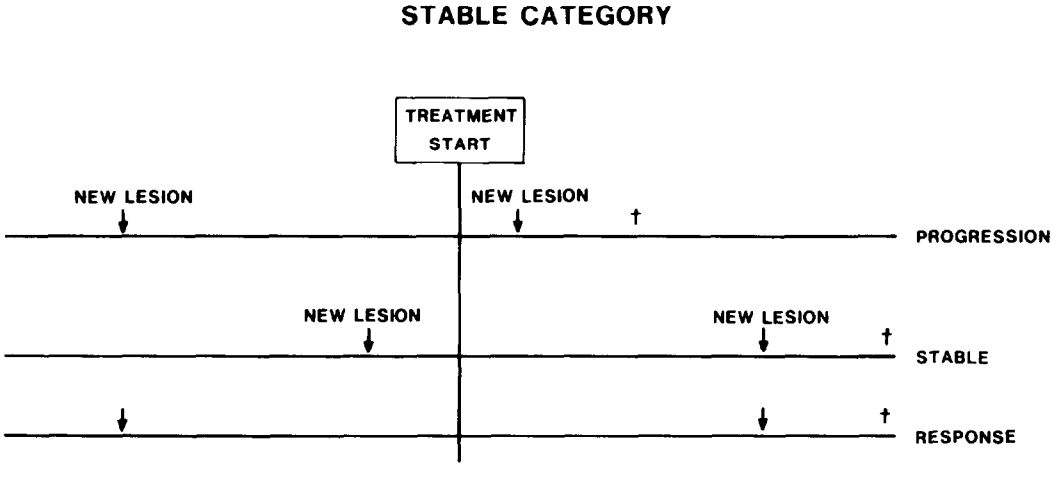

Fig. 1. Illustration of how the similar survival pattern for the stable category and the responding category in relation to start of treatment is not necessarily an expression of response to therapy for the stable category as previously claimed [23]. An alternative explanation might be that the stable category is a selected subgroup of patients from the non-responding category and similarity with the responding category in survival pattern is an expression of a displacement of the time of progression (new lesion) in relation to the start of observation (treatment start). The figure shows that the survival of the stable category is similar to the progression category seen in relation to the time of progression, but also similar to the response category if it is seen in relation to the start of treatment despite a shorter survival when it is seen in relation to the time of progression.

fore not a true reflection of therapeutic effect. Before concluding that the stable category is a subgroup of the response category, it is important to describe the progression rate before the start of treatment.

From the above speculations, several issues should be *prospectively* examined.

1. The frequency of clinically detectable metastases (osseous only, soft tissue only, soft tissue ± osseous).
2. The frequency of detectable pelvic and retroperitoneal masses on CT scan, and the usefulness of these as response parameters.
3. The technical bone scan to scan variation in the same patients, including intra- and interobserver variability.
4. Implications of the magnitude of acid phosphatase in relation to response.
5. Day to day variation in bone pain before treatment start in individual patients with bone metastases.
6. Sequential bilateral iliac crest bone biopsies before and during treatment in order to define complete response in bone metastatic disease.
7. Evaluation of the usefulness of the criteria and methods used for evaluation of the response judged by the impact of the single criterion on prognosis.

Because of the variety of response criteria and ways of reporting results, it is difficult to interpret and relate the different studies. Therefore it is proposed that the reporting of results should be standardized. The following should be reported for *phase II* studies:

1. Previous therapy.
2. Specification of metastatic sites—local disease.
3. Definition of response criteria.
4. Documentation separately of response of:
   soft tissue (location and technique)
   bone: scan
   roentgenograms
   bone marrow
   acid phosphatase (level)
   bone pain
5. Response duration, the method by which disease progression was assessed and the frequency of disease evaluation.
6. Sufficient pain evaluation (degree of pain before treatment and degree of reduction).
7. Correlations between response parameters.
8. Other palliation during protocol treatment.

For *phase III* studies, the following should be reported:

1. Stratification according to prognostic factors.
2. Survival
   Metastases free interval
   Time to progression
   Response
3. Response to secondary treatment that might have affected survival.
4. Number of deaths not caused by prostate cancer.

Only by using such detailed response documentation will it be possible to judge the value of the individual studies.

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